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PRINCIPAL INVESTIGATOR: Dr. Sue Ann Ingles

CONTRACTING ORGANIZATION: University of Southern California
Los Angeles CA 90089-1147

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Dr. Sue Ann Ingles

E-Mail: ingles@usc.edu

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14. ABSTRACT
Dietary fat has been implicated as a potential promotional factor leading to progression of small, latent, non-metastatic prostate tumors to invasive, metastatic lesions. One possible mechanism is conversion of the n-6 polyunsaturated fatty acids to inflammatory compounds produced by the lipoxygenase (LOX) family of enzymes.We are examining whether genetic variants in the n-6 fatty acid LOX pathways are associated with the risk of prostate cancer in a population-based case control study of advanced prostate cancer among African-Americans and whites in Los Angeles County. In the first two years of the study, we genotyped five LOX gene polymorphisms, including 12-LOX Gln261Arg and Ser322Asn, 15-LOX-2 Gln656Arg, 5-LOX Lys254Glu, and the 5-LOX promoter Sp1 motif polymorphism. Preliminary analyses indicate that the 12-LOX gene Gln261Arg polymorphism may be related to prostate cancer risk in both African-Americans and whites. In the third year, we will investigate whether genetic variation in specific LOX pathways, in combination with diet, contributes to prostate cancer risk. Our findings could provide a scientific foundation upon which to design dietary intervention trials and may allow us to design strategies for reducing the disparity in prostate cancer burden between African-Americans and other ethnic groups.

15. SUBJECT TERMS
None provided.

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Introduction:

Other than age, the strongest risk factor for prostate cancer is ethnicity and country of residence. African-Americans have higher mortality from prostate cancer than do other ethnic groups ("Cancer in California 1988-1997", California Cancer Registry, June 2000). It has been suggested that prostate cancer grows at a faster rate and exhibits more aggressive behavior in African-Americans (Powell and Meyskens, 2001). Dietary fat has been implicated as a potential promotional factor leading to progression of small, latent, non-metastatic prostate tumors to invasive, metastatic lesions (Snowden et al, 1984; West et al, 1991; Giovannucci et al, 1993). One mechanism by which fats might promote carcinogenesis is by conversion to eicosaoids, inflammatory compounds produced from n-6 polyunsaturated fatty acids by the lipoxygenase (LOX) family of enzymes (Steele et al, 1999). We hypothesize that dietary n-6 fatty acids, in combination with genetic variants in n-6 fatty acid LOX pathways may influence the development and progression of prostate cancer. Our specific aims are (1) to determine whether LOX genotypes are associated with risk of advanced prostate cancer in African-Americans and whites; (2) to determine whether LOX polymorphisms modify the effect of dietary fat intake on prostate cancer risk. We will test our hypotheses in a population-based case control study of advanced prostate cancer being conducted among African-Americans and whites in Los Angeles County. Using DNA samples for 860 cases (360 African-American and 500 whites) and 520 controls (230 African-American and 290 whites), we will genotype polymorphisms in lipoxygenase (LOX) family genes (5-LOX, 12-LOX and 15-LOXs). Logistic regression will be used to estimate odds ratios and test for effects of genotype and diet-genotype interaction. If we find that genetic variation in specific LOX pathways contributes to prostate cancer risk, this evidence will point to specific components of high fat diets that may increase risk. Such a finding will provide a scientific foundation upon which to design dietary intervention trials and may allow us to design strategies for reducing the disparity in prostate cancer burden between African-Americans and other ethnic groups.

Body:

In the approved Statement of Work, we proposed to finish Task 1 within the first 24 months funding (1 Dec 2003-30 Nov 2005). Task 1 has been completed, as detailed in the previous annual report.

In the final year of funding, we proposed to finish Task 2 (below). We were granted a no-cost extension (to Nov 30, 2007) to finish the final year's work.

Task 2. Data analysis and manuscript preparation (Months 25-36)

- a Create analytic dataset from original datasets (Month 25-26)
- b Analyze associations between LOX genotypes and risk of advanced prostate cancer (Month 27-28)
- c Analyze the interaction between LOX genotypes and dietary fat intake in terms of prostate cancer risk (Month 29-30)
- d Manuscript preparation (Month 31-36)

<u>To address task a:</u>

We have created analytic datasets for genotype variables and basic demographics (age, ethnicity, disease status).

To address task b:
Main effect of LOX genotypes have been assessed. Results are given in the following tables.

12-LOX Gln261Arg:
Minor allele frequencies were 32% among African-American controls and 42% among white controls. Odds ratios for the association between genotype and prostate cancer risk were remarkably similar for the two ethnic groups (see table below). Compared to men carrying the GG genotype, men carrying AA appeared to have an approximate 22-23% (non-significant) reduction in risk. Men with the AG genotype were similar to the baseline group (GG).

African-Americans

	Controls	Cases	OR (95% CI)
GG	75 (46%)	172 (46%)	1.00
AG vs. GG	69 (43%)	169 (45%)	1.07 (0.72, 1.58)
AA vs. GG	18 (11%)	32 (9%)	0.78 (0.41, 1.47)
AA vs. GG+AG			0.75 (0.41, 1.38)
Total	162 (100%)	373 (100%)	

Whites

	Controls	Cases	OR (95% CI)
GG	113 (37%)	185 (37%)	1.00
AG vs. GG	132 (43%)	235 (47%)	1.09 (0.79, 1.49)
AA vs. GG	64 (21%)	81 (18%)	0.77 (0.52, 1.16)
AA vs. GG+AG			0.74 (0.51, 1.06)
Total	309 (100%)	501 (100%)	

For the two ethnic groups combined, the reduced risk associated with the AA genotype was statistically significant. Compared to men carrying the GG or GA genotypes, men carrying AA had an approximate 30% reduction in risk (see table below).

All men (African Americans & Whites)

	Controls	Cases	OR (95% CI)
GG	188 (40%)	357 (41%)	1.00
AG vs. GG	201 (43%)	404 (46%)	1.06 (0.83, 1.35)
AA vs. GG	82 (17%)	113 (13%)	0.73 (0.52, 1.01)
AA vs. GG+AG			0.70 (0.52, 0.96)
Total	471 (100%)	874 (100%)	

12-LOX Ser322Asn:
Minor allele frequencies were 19% among African-American controls and 42% among white controls. The Ser322Asn polymorphism was in tight LD with the Gln261Arg in whites, hence among whites the odds ratios for Gln261arg were nearly identical to those for Ser322Asn. Among African-Americans, the two polymorphisms were not in tight LD. The Ser322Asn polymorphism was not associated with risk in African-Americans.

African-Americans

	Controls	Cases	OR (95% CI)
AA	108 (67%)	236 (63%)	1.00
AG	47 (29%)	123 (33%)	1.20 (0.80, 1.80)

GG	7 (4%)	14 (4%)	0.92 (0.36, 2.33)
Total	162 (100%)	373 (100%)	

Whites

	Controls	Cases	OR (95% CI)
AA	113 (37%)	189 (38%)	1.00
AG	133 (43%)	231 (46%)	1.04 (0.76, 1.42)
GG	63 (20%)	81 (16%)	0.77 (0.51, 1.15)
Total	309 (100%)	501 (100%)	

5-LOX gene Sp1:
The genotypes are summarized in the following table.

	African-American		Whites	
	Controls	Cases	Controls	Cases
2 / 4	1 (1%)	0 (0%)	0 (0%)	0 (0%)
2 / 5	0 (0%)	0 (0%)	1 (0%)	0 (0%)
3 / 3	15 (9%)	37 (10%)	0 (0%)	0 (0%)
3 / 4	10 (6%)	32 (9%)	0 (0%)	0 (0%)
3 / 5	42 (26%)	109 (30%)	2 (1%)	4 (1%)
3 / 6	3 (2%)	8 (2%)	0 (0%)	0 (0%)
3 / 7	0 (0%)	1 (0%)	0 (0%)	0 (0%)
4 / 4	9 (6%)	9 (2%)	7 (2%)	11 (2%)
4 / 5	31 (19%)	67 (18%)	81 (26%)	132 (27%)
4 / 6	2 (1%)	5 (1%)	1 (0%)	0 (0%)
4 / 7	0 (0%)	1 (0%)	0 (0%)	0 (0%)
5 / 5 (wildtype)	44 (28%)	85 (23%)	207 (67%)	337 (68%)
5 / 6	3 (2%)	8 (2%)	8 (3%)	11 (2%)
5 / 7	0 (0%)	7 (2%)	0 (0%)	3 (1%)
Total	160 (100%)	369 (100%)	307 (100%)	498 (100%)

5-LOX Lys254Glu:
This polymorphism was not genotyped in whites since it is rare in subjects of non-African ancestry. This polymorphism was not associated with prostate cancer risk.

African-Americans

	Controls	Cases	OR (95% CI)
GG	136 (84%)	308 (83%)	1.00
AG vs. GG	26 (16%)	63 (17%)	1.07 (0.65, 1.76)
AA vs. GG	0 (0%)	2 (1%)	
AA vs. GG+AG			1.10 (0.67, 1.82)
Total	162 (100%)	373 (100%)	

1**5-LOX-2 gene Gln656Arg:**
This polymorphism was not significantly associated with prostate cancer risk in African-

Americans or whites.

African-Americans

	Controls	Cases	OR (95% CI)
CC	102 (63%)	233 (63%)	1.00
CT	49 (30%)	125 (34%)	1.12 (0.75, 1.67)
TT	11 (7%)	14 (4%)	0.56 (0.24, 1.27)
Total	162 (100%)	372 (100%)	

Whites

	Controls	Cases	OR (95% CI)
CC	86 (28%)	130 (26%)	1.00
CT	148 (48%)	243 (49%)	1.09 (0.77, 1.53)
TT	74 (24%)	128 (26%)	1.14 (0.77, 1.70)
Total	308 (100%)	501 (100%)	

To address task c:
We are preparing the analytic dataset containing variables from the prostate cancer risk factor questionnaire. We have recently finished data entry of over 1800 questionnaires. Data are being cleaned, and will be shipped to our collaborator at the Northern California Cancer Center (Dr. Esther John) for processing of dietary data to generate variables on dietary fat intake from the food frequency questionnaire. We will then merge these variables to the current analytic dataset (created in task a) and will be able to analyze interactions between genotypes and dietary fat.

To address task d:
Not yet done.

Key Research Accomplishments

Preliminary analyses indicate that the 12-LOX gene Gln261Arg polymorphism may be related to prostate cancer risk in both African-Americans and whites.

Reportable Outcomes:

None to date. (Pending final analyses)

Conclusions:

None to date. (Pending final analyses)

References

Giovannucci E. Rimm EB. Colditz GA. Stampfer MJ. Ascherio A. Chute CC. Willett WC. A prospective study of dietary fat and risk of prostate cancer. Journal of the National Cancer Institute. 85(19): 1571-9, 1993

Powell IJ, Meyskens FL Jr. African American men and hereditary/familial prostate cancer: Intermediate-risk populations for chemoprevention trials. Urology 57(4 Suppl 1): 178-81. 2001

Snowdon DA. Phillips RL. Choi W. Diet, obesity, and risk of fatal prostate cancer. American Journal of Epidemiology. 120(2): 244-50, 1984

Steele VE. Holmes CA. Hawk ET. Kopelovich L. Lubet RA. Crowell JA. Sigman CC. Kelloff GJ. Lipoxygenase inhibitors as potential cancer chemopreventives. [Review] Cancer Epidemiology, Biomarkers & Prevention. 8(5): 467-83, 1999

West DW. Slattery ML. Robison LM. French TK. Mahoney AW. Adult dietary intake and prostate cancer risk in Utah: a case-control study with special emphasis on aggressive tumors. Cancer Causes & Control. 2(2): 85-94, 1991

Appendices

None